

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Applicants : Pasternak et al.  
Serial No. : Division of U.S. Application Serial No. 09/743,871  
Filed : herewith  
For : IDENTIFICATION AND CHARACTERIZATION OF MULTIPLE SPLICE  
VARIANTS OF THE KAPPA<sub>3</sub>-RELATED OPIOID RECEPTOR (KOR-3) GENE

Group Art Unit: Not assigned

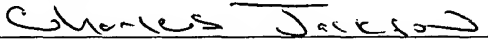
745 Fifth Avenue  
New York, New York 10151

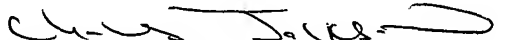
**EXPRESS MAIL**

Mailing Label Number: EV 345013121US

Date of Deposit: June 26, 2003

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" Service under 37 CFR 1.10 on the date indicated above and is addressed to: Assistant Commissioner for Patents, Washington, DC 20231.

  
(Typed or printed name of person mailing paper or fee)

  
(Signature of person mailing paper or fee)

**INFORMATION DISCLOSURE STATEMENT**

Assistant Commissioner for Patents  
Box Patent Application  
Washington, D.C. 20231

Dear Sir:

The Examiner's attention is respectfully directed to the documents which are set forth on the accompanying form PTO-1449. Since these documents were forwarded to or cited by the Examiner in the parent application, U.S. Serial No. 09/743,871, filed March 13, 2001, and a copy of each of these documents should be in the parent application file, no additional copy is being forwarded with this Information Disclosure Statement.

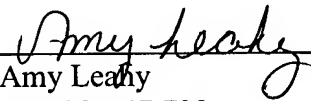
As this Information Disclosure Statement is being filed before the mailing of the first Office Action on the merits, it is believed that no fee is required for entry of this paper.

However, the Commissioner is hereby authorized to charge any such fee, or credit any overpayment to Deposit Account 50-0320.

The filing of this Information Disclosure Statement is not an admission that the documents identified herein constitute prior art to the present application.

Applicants respectfully request that the Examiner considers and makes of record the documents cited herewith and that a copy of Form PTO-1449 be initialed by the Examiner and returned to the undersigned.

Respectfully submitted,  
FROMMER LAWRENCE & HAUG LLP  
Attorneys for Applicant

  
\_\_\_\_\_  
Amy Leahy  
Reg. No. 47,739  
(212) 588-0800

Based on Form PTO-1449	ATTY. DOCKET NO.: 830002-2001.1	SERIAL NO.: 09/743,871
LIST OF REFERENCES CITED BY APPLICANT	APPLICANT: Pasternak et al.	
	FILING DATE: January 16, 2001	GROUP ART UNIT 1646

## FOREIGN PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION	
							YES	NO
	CN	WO 95/12616	05/11/95	WIPO				
	CO	WO 94/28132	12/08/94	WIPO				

## OTHER ART (Including Author, Title, Date, Pertinent Pages, Etc.)

	CP	Nishi et al. (1994) "Structure and chromosomal mapping of genes for the mouse kappa-opioid receptor and an opioid receptor homologue (MOR-C)" Biochem. Biophys. Res. Commun. 205:1353-1357
	CQ	Pan et al. (1996) "Mus musculus opioid receptor (KOR-3) gene, exon 1" Database EMBL-EMROD (Online) Entry MMUOR3SO2, Acc. No. U32926
	CR	Pan et al. (1996) "Mus musculus opioid receptor (KOR-3) gene, exon 2" Database EMBL-EMROD (Online) Entry MMUOR3SO4, Acc. No. U 32928
	CS	Pan et al. (1996) "Mus musculus opioid receptor (KOR-3) gene, exon 3" Database EMBL-EMROD (Online) Entry MMUOR3SO6, Acc. No. U 32930
	CT	Pan et al. (1998) "Identification and differential regional expression of KOR-3/ORL-1 gene splice variants in mouse brain" FEBS Lett. 435:65-68
	CU	Pasternak et al. (1996) "the KOR-3 receptor and the kappa3-opioid receptor may be splice variants of the same gene" Trends Pharm. Sci. 17:217-218
	CV	Peluso et al. (1997) "Distribution of nociceptin/orphanin FQ receptor transcript in human central nervous system and immune cells" J. Neuroimmunol. 81:184-192
	Cw	European Search Report September 17, 2001

EXAMINER	DATE CONSIDERED
<p>* EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.</p>	

Based on Form PTO-1449 (3/90)				ATTY. DOCKET NO.  <b>830002-2001.1</b>		SERIAL NO.  <b>09/743,871</b>	
LIST OF REFERENCES CITED BY APPLICANT (Use several sheets if necessary)				APPLICANT  <b>Pasternak et al.</b>			
				FILING DATE  <b>January 16, 2001</b>		GROUP  <b>1646</b>	
U.S. PATENT DOCUMENTS							
EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
FOREIGN PATENT DOCUMENTS							
		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION
							YES NO
	AA	WO 94/28132	12/8/94	WIPO			
	AB	WO 95/12616	5/11/95	WIPO			
OTHER PRIOR ART (Including Author, Title, Date, Pertinent Pages, Etc.)							
	AC	Pan et al. Genbank Accession U32928, 28 July 1996					
	AD	Pan et al. Genbank Accession U32930, 28 July 1996					
	AE	Nishi, m. et al. "structure and chromosomal mapping of genes for the mouse kappa-opioid receptor homologue (MOR-C) Biochemical and Biophysical research communications, vol. 205(2), 1353-1357, 15 December 1994					
	AF	Ying-Xian et al. "Identification and differential regional expression of KOR-3/ORL-1 gene splice variants in mouse brain" FEBS Letters 435 (1998) 65-68					
	AG	Peluso et al. "Distribution of nociceptin/orphanin FQ receptor transcript in human central nervous system and immune cells" Journal of Neuroimmunology 81 (1998) 184-192.					
	AH	Pan et al., Genbank Accession U32926. August 1995					
	AI	Reinscheid, RK et al. Science 270, 790-794, 1995					
	AJ	Meunier, JC et al. Nature 377, 532-535, 1995					
	AK	Pan, Y-X, et al. FEBS Letters, 395, 207-210, 1996					
	AL	Mathis JP et al. Biochem Biophys res. Commun, 230, 462-465, 1997.					
	AM	Halford, WP et al. "Functional role and sequence analysis of a lymphocyte orphan opioid receptor." Journal of Neuroimmunology, vol. 59, 91-101, 1995					
	AN	Pan et al. "Cloning and functional characterization through antisense mapping of a kappa3-related opioid receptor" Molecular Pharmacology, vol. 47, June 1995, pages 1180-8.					
	AO	Wang, J.B. et al. "cDNA cloning of an orphan opiate receptor gene family member and its splice variant" FEBS letters, vol. 348, 75-79, 1994					
	AP	Pasternak et al. "Pasternak and Standiford reply- The KOR3 receptor and the kappa3-opioid receptor may be splice variants of the same gene" Trends in Pharmacological Sciences, GB, Elsevier Trends Journal, Cambridge, vol. 17, no. 6, 217-218, 1 June 1996					
	AQ	Mollereau, C. et al. "ORL1, a novel member of the opioid receptor family. Cloning, functional expression and localization." FEBS, vol. 341, 33-38, 1994.					
EXAMINER				DATE CONSIDERED			
* EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.							

Based on Form PTO-1449		ATTY. DOCKET NO.: 830002-2001.1		SERIAL NO.: 09/743,871	
LIST OF REFERENCES CITED BY APPLICANT		APPLICANT: Pasternak et al.			
		FILING DATE: January 16, 2001		GROUP ART UNIT	
<b>U.S. PATENT DOCUMENTS</b>					
EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS
	AA	4,946,778	08/07/90	Ladner et al.	
	AB	5,747,279	05/05/98	Pasternak et al.	
<b>OTHER PRIOR ART (Including Author, Title, Date, Pertinent Pages, Etc.)</b>					
	AC	Bare et al. (1994) "Expression of two variants of the human $\mu$ opioid receptor mRNA in SK-N-SH cells and human brain" FEBS Lett. 354:213-6			
	AD	Bunzow et al. (1994) "Molecular cloning and tissue distribution of a putative member of the rat opioid receptor gene family that is not a $\mu$ , $\delta$ or $\kappa$ or an opioid receptor type" FEBS Lett. 347:284-288			
	AE	Capecchi (1989) "Altering the genome by homologous recombination" Science 244:1288			
	AF	Chen et al. (1993) "Molecular cloning and functional expression of a $\mu$ -opioid receptor from rat brain" Mol. Pharmacol. 44:8-12			
	AG	Chomczynski et al. (1987) "Single-step method of RNA isolation by acid guanidinium thiocyanate-phenol-chloroform extraction" Anal. Biochem. 162:156-9			
	AH	Cole et al. (1985) "The EBV-hybridoma technique and its application to human lung cancer" in "Monoclonal Antibodies and Cancer Therapy" Alan R. Liss, Inc., pp. 77-96			
	AI	Cote et al. (1983) "Generation of human monoclonal antibodies reactive with cellular antigens" Proc. Natl. Acad. Sci. U.S.A. 80:2026-2030			
	AJ	Delfs et al. (1994) "Expression of $\mu$ opioid receptor mRNA in rat brain: an in situ hybridization study at the single cell level" J. Comp. Neurol. 345:46-68			
	AK	Elliott et al. (1994) "The NMDA receptor antagonists, LY274614 and MK-801, and the nitric oxide synthase inhibitor, NG-nitro-L-arginine, attenuate analgesic tolerance to the $\mu$ -opioid morphine but not to kappa opioids" Pain 56:69-75			
	AL	Evans et al. (1981) "Establishment in culture of pluripotential cells from mouse embryos" Nature 292:154-6			
	AM	Fukuda et al. (1994) "cDNA cloning and regional distribution of a novel member of the opioid receptor family" FEBS Lett. 343:42-46			
	AN	Gaveriaux-Ruff et al. (1997) "Detection of opioid receptor mRNA by RT-PCR reveals alternative splicing for the $\delta$ and $\kappa$ -opioid receptors" Molec. Brain Res. 48:298-304			
EXAMINER			DATE CONSIDERED		
<p>* EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.</p>					

Based on Form PTO-1449		ATTY. DOCKET NO.: 830002-2001.1	SERIAL NO.: 09/743,871
LIST OF REFERENCES CITED BY APPLICANT		APPLICANT: Pasternak et al.	
		FILING DATE: January 16, 2001	GROUP ART UNIT
	AO	Grisel et al. (1996) "Orphanin FQ acts as a supraspinal, but not a spinal, anti-opioid peptide" NeuroReport 7:2125-2129	
	AP	Guiramand et al. (1995) "Alternative splicing of the dopamine D2 receptor directs specificity of coupling to G-proteins" J. Biol. Chem. 270:7354-58	
	AQ	Halford et al. (1995) "Functional role and sequence analysis of a lymphocyte orphan opioid receptor" J. Neuroimmunol. 59:91-101	
	AR	Huse et al. (1989) "Generation of a large combinatorial library of the immunoglobulin repertoire in phage lambda" Science 246:1275-81	
	AS	Jaenisch (1988) "Transgenic animals" Science 240:1468-74	
	AT	King et al. (1998) "Functional blockade of opioid analgesia by orphanin FQ/nociceptin" Biochem. Pharmacol. 55:1537-40	
	AU	King et al. (1997) "Spinal analgesic activity of orphanin FQ/nociceptin and its fragments" Neurosci. Lett. 223:113-116	
	AV	Kohler et al. (1975) "Continuous cultures of fused cells secreting antibody of predefined specificity" Nature 256:495	
	AW	Kolesnikov et al. (1994) "1-Aminocyclopropane carboxylic acid (ACPC) prevents $\mu$ and $\delta$ opioid tolerance" Life Sci. 55:1393-98	
	AX	Kolesnikov et al. (1993) "Blockade of tolerance to morphine but not to kappa opioids by a nitric oxide synthase inhibitor" Proc. Natl. Acad. Sci. U.S.A. 90:5162-5166	
	AY	Kozbor et al. (1983) "The production of monoclonal antibodies from human lymphocytes" Immunol. Today 4:72	
	AZ	Lucas et al. (1995) "New players in the 5-HT receptor field: genes and knockouts" TIPS 16:246-252	
	BA	Lutz et al. (1992) "Opioid receptors and their pharmacological profiles" J. Receptor Res. 12:267-286	
	BB	Mathis et al. (1997) "Biochemical evidence for orphanin FQ/nociceptin receptor heterogeneity in mouse brain" Biochem. Biophys. Res. Commun. 230:462-5	
	BC	McCullough et al. (1997) "G triplets located throughout a class of small vertebrate introns enforce intron borders and regulate splice site selection" Molec. Cell. Biol. 17:4562-4571	
	BD	Meunier et al. (1995) "Isolation and structure of the endogenous agonist of opioid receptor-like ORL <sub>1</sub> receptor" Nature 377:532-535	

EXAMINER	DATE CONSIDERED
<p>* EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.</p>	

Based on Form PTO-1449		ATTY. DOCKET NO.: 830002-2001.1	SERIAL NO.: 09/743,871
LIST OF REFERENCES CITED BY APPLICANT		APPLICANT: Pasternak et al.	
		FILING DATE: January 16, 2001	GROUP ART UNIT
	BE	Mogil et al. (1996) "Functional antagonism of $\mu$ , $\delta$ - or $\kappa$ -opioid antinociception by orphanin FQ" Neurosci. Lett. 214:1-4	
	BF	Mogil et al. (1996) "Orphanin FQ is a Functional Anti-Opioid Peptide" Neurosci. 75:333-337	
	BG	Mollereau et al. (1994) "ORL1, a novel member of the opioid receptor family" FEBS Lett. 341:33-38	
	BH	Morrison et al. (1984) "Chimeric human antibody molecules: mouse antigen-binding domains with human constant region domains" Proc. Natl. Acad. Sci. U.S.A. 81:6851-55	
	BI	Neuberger et al. (1984) "Recombinant antibodies possessing novel effector functions" Nature 312:604-8	
	BJ	Olson et al. (1989) "Endogenous opiates: 1988" Peptides 10:1253-1280	
	BK	Pan et al. (1996) "Structure and characterization of gene encoding a mouse kappa <sub>3</sub> -related opioid receptor" Gene 171:255-260	
	BL	Pan et al. (1996) "Dissociation of affinity and efficacy in KOR-3 chimeras" FEBS Lett. 395:207-10	
	BM	Pan et al. (1995) "Cloning and Functional Characterization Through Antisense Mapping of a $\kappa_3$ -Related Opioid Receptor" Mol. Pharmacol. 47:1180-1188	
	BN	Pan et al. (1994) "Cloning, expression and classification of a Kappa3 -related opioid receptor using antisense oligodeoxynucleotides" Regul. Pept. 54:217-218	
	BO	Pasternak et al. (1995) "Mapping of opioid receptors using antisense oligodeoxynucleotides: correlating their molecular biology and pharmacology" TiPS 16:344-50	
	BP	Pasternak (1993) "Pharmacological mechanisms of opioid analgesics" Clin. Neuropharmacol. 16:1-18	
	BQ	Reinscheid et al. "Orphanin FQ: A neuropeptide that activates an opioidlike G protein-coupled receptor" (1995) Science 270:792-794	
	BR	Reisine et al. (1996) "Opioid analgesics and antagonists" in Goodman & Gilman's "The pharmacological basis of therapeutics" Ninth Edition (Hardman et al. eds.) McGraw-Hill pp. 521-555	
	BS	Reisine et al. (1993) "Molecular Biology of opioid receptors" Trends Neurosci. 16:506-510	

EXAMINER	DATE CONSIDERED
<p>* EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.</p>	

Based on Form PTO-1449		ATTY. DOCKET NO.: 830002-2001.1	SERIAL NO.: 09/743,871
LIST OF REFERENCES CITED BY APPLICANT		APPLICANT: Pasternak et al.	
		FILING DATE: January 16, 2001	GROUP ART UNIT
	BT	Robertson (1991) "Using embryonic stem cells to introduce mutations into the mouse germ line" Biol. Reprod. 44:238-245	
	BU	Rossi et al. (1997) "Antisense mapping of MOR-1 in rats: distinguishing between morphine and morphine-6 $\beta$ -glucuronide antinociception" J. Pharmacol. Exp. Ther. 281:109-114	
	BV	Rossi et al. (1994) "Blockade of Morphine Analgesia by an Antisense Oligodeoxynucleotide Against the Mu Receptor" Life Sci. 54:375-379	
	BW	Rossi et al. (1996) "Novel receptor mechanisms for heroin and morphine-6 $\beta$ -glucuronide analgesia" Neurosci. Lett. 216:1-4	
	BX	Rossi et al. (1996) "Naloxone sensitive orphanin FQ-induced analgesia in mice" Eur. J. Pharmacol. 311:R7-8	
	BY	Sibinga et al. (1988) "Opioid peptides and opioid receptors in cells of the immune system" Annu. Rev. Immunol. 6:219-49	
	BZ	Simon (1991) "Opioid receptors and endogenous opioid peptides" Med. Res. Rev. 11:357-374	
	CA	Standifer et al. (1997) "G proteins and opioid receptor-mediated signaling" Cell. Signal. 9:237-248	
	CB	Standifer et al. (1996) "Differential blockade of opioid analgesia by antisense oligodeoxynucleotides directed against various G protein $\alpha$ subunits" Mol. Pharmacol. 50:293-298	
	CC	Takeda et al. (1985) "Construction of chimaeric processed immunoglobulin genes containing mouse variable and human constant region sequences" Nature 314:452-4	
	CD	Tian et al. (1997) "Bidirectional modulatory effect of orphanin FQ on morphine-induced analgesia: antagonism in brain and potentiation in spinal cord of the rat" Br. J. Pharmacol. 120:676-80	
	CE	Trujillo et al. (1991) "Inhibition of morphine tolerance and dependence by the NMDA receptor antagonist MK-801" Science 251:85-87	
	CF	van den Engh et al. (1992) "Estimating genomic distance from DNA sequence location in cell nuclei by a random walk model" Science 257:1410-1412	
	CG	Vanetti et al. (1992) "Cloning and expression of a novel mouse somatostatin receptor (SSTR2B)" FEBS Lett. 311:290-294	
	CH	Wang, et al. (1994) "cDNA cloning of an orphan opiate receptor gene family member and its splice variant" FEBS Lett. 348:75-9	
EXAMINER		DATE CONSIDERED	
<p>* EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.</p>			



Based on Form PTO-1449		ATTY. DOCKET NO.: 830002-2001.1	SERIAL NO.: 09/743,871
LIST OF REFERENCES CITED BY APPLICANT		APPLICANT: Pasternak et al.	
		FILING DATE: January 16, 2001	GROUP ART UNIT
	CI	Wick et al. (1994) "Isolation of novel cDNA encoding a putative membrane receptor with high homology to the cloned $\mu$ , $\delta$ and $\kappa$ opioid receptors" Molec. Brain Res. 27:37-44	
	CJ	Yamamoto et al. (1997) "Analgesic Effect of Intrathecally Administered Nociceptin, an Opioid Receptor-Like <sub>1</sub> Receptor Agonist, in the Rat Formalin Test" Neurosci. 81:249-254	
	CK	Yasuda et al. (1993) "Cloning and functional comparison of $\kappa$ and $\delta$ opioid receptors from mouse brain" Proc. Natl. Acad. Sci. U.S.A. 90:6736-6740	
	CL	Zhu et al. (1997) "Orphanin FQ potentiates formalin-induced pain behavior and antagonizes morphine analgesia in rats" Neurosci. Lett. 235:37-40	
	CM	Zimprich et al. (1995) "Cloning and expression of an isoform of the rat $\mu$ opioid receptor (rMOR1B) which differs in agonist induced desensitization from RmOR1" FEBS Lett. 359:142-146	

EXAMINER	DATE CONSIDERED
<p>* EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.</p>	